



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 209/34, A61K 31/395, C07D 491/04, 471/04, 401/06	A1	(11) International Publication Number: WO 95/14667 (43) International Publication Date: 1 June 1995 (01.06.95)
(21) International Application Number: PCT/IB94/00312 (22) International Filing Date: 12 October 1994 (12.10.94) (30) Priority Data: 08/164,973 26 November 1993 (26.11.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/164,973 (CON) Filed on 26 November 1993 (26.11.93) (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): MASAMUNE, Hiroko [US/US]; 68 High Street, Noank, CT 06340 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: SUBSTITUTED INDOLES AS PHOSPHODIESTERASE TYPE IV INHIBITORS <div data-bbox="565 1129 1003 1423" data-label="Chemical-Block"></div> <div data-bbox="1170 1268 1198 1297" data-label="Text">(I)</div>		
(57) Abstract <p>The present invention relates to novel substituted oxindoles of formula (I), as defined in the description, and related compounds, pharmaceutical compositions comprising such compounds, and the use of such compounds as inhibitors of phosphodiesterase ("PDE") type IV. The compounds of this invention are useful in the treatment of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, other inflammatory diseases, and other conditions where the action of phosphodiesterase type IV is implicated.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LO	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

-1-

5 SUBSTITUTED INDOLES AS PHOSPHODIESTERASE TYPE IV INHIBITORS

Background of the Invention

10 The present invention relates to novel substituted oxindoles and related compounds, pharmaceutical compositions comprising such compounds, and the use of such compounds as inhibitors of phosphodiesterase ("PDE") type IV. The compounds of this invention are useful in the treatment of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases. This invention also relates to pharmaceutical compositions containing these compounds and to methods of inhibiting the action of phosphodiesterase type IV.

15 Since the recognition that cyclic adenosine monophosphate ("cAMP") is an intracellular second messenger (E.W. Sutherland and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of phosphodiesterases has been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. Distinct classes of phosphodiesterases have been recognized (J. A. Beavo and D. H. Reifsnyder, TIPS, 20 1990, 11, 150) and their selective inhibition has led to improved drug therapies (C. D. Nicholson, R. A. Challiss, and M. Shahid, TIPS, 1991, 12, 19). It has been claimed that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M. W. Verghese, et al., J. Mol. Cell Cardiol., 1989, 12 (Supp. II), S 61) and airway smooth muscle relaxation (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds. S. R. 25 O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag).

Certain pyrimidone compounds have been described as antidepressants in EP 0 247 725 A2, published December 2, 1987. Certain pyrimidone compounds have been described as useful against asthma and certain skin disorders in WO 91/07178 published May 30, 1991.

30 The following documents relate to inhibitors of phosphodiesterase type IV: WO 87/06576, published November 5, 1987; WO 91/15451, published October 17, 1991; WO 91/16303, published October 31, 1991; WO 92/00968, published January 23, 1992; WO 92/07567, published May 14, 1992; WO 92/12961, published August 6, 1992; EP 0 428 313 A2, published May 22, 1991; EP 0 442 204 A2, published August 21, 1991; 35 EP 0 470 805 A1, published February 12, 1992; EP 0 473 963 A1, published March 11, 1992; EP 0 497 564 A1, published August 5, 1992; EP 0 511 865 A1, published November 4, 1992; and EP 0 303 418 A2, published February 15, 1989. The following

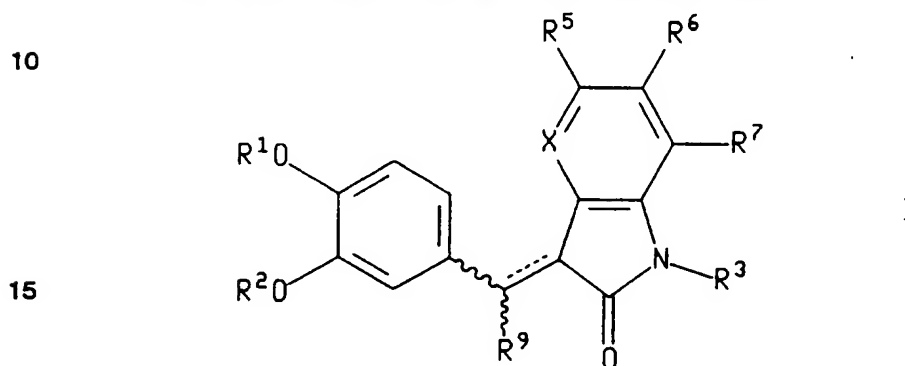
-2-

documents relate to inhibitors of phosphodiesterase type IV in non-pulmonary/non-allergic uses: US 4,582,834, issued April 15, 1986; US 4,971,959, issued November 20, 1990; US 5,077,290, issued December 31, 1991; DE 3742716 A1, published June 22, 1989; and DE 4027592 A1, published March 5, 1992.

5 All documents cited herein, including the foregoing, are incorporated herein by reference in their entireties.

Summary of the Invention

The present invention relates to a compound of the formula:



wherein X is N or CR⁴;

R¹ is (C₁-C₄) alkyl or phenyl-(C₁-C₆) alkyl;

20 R² is (C₁-C₁₀) alkyl, phenyl-(C₁-C₆) alkyl, (C₃-C₇) cycloalkyl, or (C₆-C₁₂) polycycloalkyl;

or R¹ and R², taken together with the oxygens to which they are attached, represent a methylene or ethylene bridge which forms a 5 or 6 membered ring;

25 R³ is hydrogen, (C₁-C₆) alkyl, (C₁-C₆) alkyloxycarbonyl, (C₁-C₆) alkyloxy, (C₁-C₆) alkoxy, (C₁-C₆) alkoxycarbonyl-(C₁-C₆) alkyl, -CONR¹⁰R¹¹; or -(C₁-C₆) alkyl-CONR¹⁰R¹¹;

R¹⁰ and R¹¹ are independently selected from hydrogen and (C₁-C₆) alkyl, or R¹⁰ and R¹¹, taken together with the nitrogen to which they are attached, form a pyrrolidine or piperidine ring;

30 R⁴, R⁵, R⁶ and R⁷ are independently selected from hydrogen, halogen, (C₁-C₆) alkoxy, (C₃-C₇) cycloalkyloxy, hydroxy, (C₂-C₆) acyloxy, nitro, NR⁸R¹², SO₂NR⁸R¹², (C₁-C₆) alkyl, (C₁-C₆) alkylcarbonyl, phenyl-(C₁-C₆)alkoxy, and (C₆-C₁₂) polycycloalkoxy or any combination of R⁴ and R⁵, R⁵ and R⁶, or R⁶ and R⁷ which together form -OCH₂O-

-3-

or $-\text{OCH}_2\text{CH}_2\text{O}-$, such that, when taken together with the carbons to which they are attached, they form, respectively, a 5- or 6-membered ring;

R^8 and R^{12} are independently selected from hydrogen and (C_1-C_6) alkyl, or R^8 and R^{12} , taken together with the nitrogen to which they are attached, form a pyrrolidine or piperidine ring;

R^9 is hydrogen or (C_1-C_6) alkyl;

the broken line represents an optional double bond; and

the wavy lines indicate that the compounds exist as (E) and/or (Z) stereoisomers when the broken line is a double bond;

with the proviso that (a) if R^1 and R^2 are both methyl, X is CH, R^9 is hydrogen, and the broken line is a double bond, then (i) at least one of R^3 , R^5 , R^6 , and R^7 is other than hydrogen; (ii) at least one of R^5 , R^6 and R^7 is other than hydrogen or R^3 is other than methyl; and (iii) at least one of R^3 and R^7 is other than hydrogen or at least one of R^5 and R^6 is other than $\text{O}-\text{CH}_3$; (b) if R^3 is hydrogen, R^9 is hydrogen, X is CH, the broken line is a double bond, and R^1 and R^2 together represent a methylene bridge, then at least one of R^5 , R^6 and R^7 is other than hydrogen; and (c) if R^1 and R^2 are both methyl, X is CH, R^9 is hydrogen, and the broken line is a single bond, then at least one of R^5 and R^6 is other than $\text{O}-\text{CH}_3$, or R^7 is other than hydrogen, or R^3 is other than COCH_3 ;

or a pharmaceutically acceptable salt thereof.

The terms "halo" or "halogen", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties, for example, methyl, ethyl, n-propyl, isopropyl and t-butyl.

The term "cycloalkyl", unless otherwise indicated, means a saturated carbocyclic radical, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "alkoxy", unless otherwise indicated, includes O-alkyl groups wherein "alkyl" is defined as above.

The term "polycycloalkyl" means a saturated carbopolycyclic radical, such as norbornyl, bicyclo[2.2.2]octyl, or adamantyl.

The term "alkyloxycarbonyl" means an alkoxy group (as defined above) attached to a carbonyl moiety.

-4-

The term "alkyloxy" means the same as alkoxy.

The term "cycloalkyloxy" includes O-cycloalkyl groups wherein cycloalkyl is defined as above.

The term "acyloxy" means an alkyl group (as defined above) attached to a carbonyl moiety which is then attached to an oxygen.

The term "alkylcarbonyl" means an alkyl group (defined as above) attached to a carbonyl moiety.

A preferred compound of the present invention is a compound of the formula I wherein R¹ is methyl or ethyl and R² is (C₁-C₆) alkyl, phenyl-(C₁-C₆) alkyl, (C₃-C₇) cycloalkyl, or (C₈-C₁₂) polycycloalkyl; or R¹ and R², taken together with the oxygens to which they are attached, represent a methylene or ethylene bridge which forms a 5 or 6 membered ring.

In a more preferred embodiment, X is CH or N, R¹ is methyl, R² is norbornyl, R³ is hydrogen, methyl, ethyl, -COOC₂H₅, -CONH₂, methoxy or -CH₂COOC₂H₅, R⁶ is hydrogen, bromo, methoxy or chloro, and R⁵ is hydrogen, hydroxy, cyclopentyloxy, methoxy, bromo, chloro, amino, or -SO₂NH₂, or R⁵ and R⁶ together form -OCH₂O-, R⁷ is hydrogen, and R⁹ is hydrogen or methyl.

Specific preferred compounds of the present invention are:

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-
20 [1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-
ethyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-
methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-
25 ethyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-chloro-1,3-
dihydro-1-methoxy-[1 α ,2 α (Z), 4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-chloro-1,3-
30 dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-
dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

-5-

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

5 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyloxy-1,3-dihydro-1-ethyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-methoxy-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one; and

10 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-2,3-dihydro-N,N-dimethyl-2-oxo-[1 α ,2 α (E),4 α]-1H-indole-5-sulfonamide.

Other compounds of the present invention include the following:

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

15 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methyl]-1,3-dihydro-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-hydroxy-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-hydroxy-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

20 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methyl]-5-hydroxy-1,3-dihydro-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-2,3-dihydro-2-oxo-[1 α ,2 α (E),4 α]-1H-indole-1-carboxylic acid, ethyl ester;

25 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-2,3-dihydro-2-oxo-[1 α ,2 α (Z),4 α]-1H-indol-1-carboxylic acid, ethyl ester;

5-Acetyloxy-3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

30 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-chloro-1,3-dihydro-1-methoxy-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyloxy-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyloxy-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-chloro-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

5 (Z)-3-[(2,3-Dihydro-1,4-benzodioxin-6-yl)methylene]-1,3-dihydro-2H-indol-2-one;

3-[(3,4-Dimethoxyphenyl)methylene]-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

(E)-3-[(2,3-Dihydro-1,4-benzodioxin-6-yl)methylene]-1,3-dihydro-2H-indol-2-one;

(E)-3-(1,3-Benzodioxol-5-ylmethylene)-1,3-dihydro-2H-indol-2-one;

10 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyloxy-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

15 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-pyrrolo[3,2-b]pyridin-2-one;

(E)-1,3-Dihydro-3-[[4-methoxy-3-(4-phenylbutoxy)phenyl]-methylene]-2H-indol-2-one;

20 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-pyrrolo[3,2-b]pyridin-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5,7-dinitro-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

25 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-nitro-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-nitro-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

30 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5,6-dimethoxy-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5,6-dimethoxy-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-nitro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-hydroxy-1,3-dihydro-1-ethyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

5 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5,7-dinitro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

5-Amino-3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxy-phenyl]methyl]-1,3-dihydro-1-methyl-2H-indol-2-one;

10 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyloxy-1,3-dihydro-1-ethyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

5-Amino-3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-pyrrolo[3,2-b]pyridin-2-one;

15 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-methoxy-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-methoxy-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

20 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-methoxy-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-methoxy-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-pyrrolo[3,2-b]pyridin-2-one;

25 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-2,3-dihydro-2-oxo-[1 α ,2 α (E),4 α]-1H-indole-1-carboxamide;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-2,3-dihydro-2-oxo-[1 α ,2 α (Z),4 α]-1H-indole-1-carboxamide;

30 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-nitro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

5-Acetyl-3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

- 5-Acetyl-3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;
- (E)-3-[(3,4-Dimethoxyphenyl)methylene]-2,3-dihydro-2-oxo-1H-indole-1-acetic acid, ethyl ester;
- 5 (Z)-3-[(3,4-Dimethoxyphenyl)methylene]-2,3-dihydro-2-oxo-1H-indole-1-acetic acid, ethyl ester;
- (E)-5-Bromo-3-[(3,4-dimethoxyphenyl)methylene]-2,3-dihydro-2-oxo-1H-indole-1-acetic acid, ethyl ester;
- 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-2,3-dihydro-N,N-dimethyl-2-oxo-[1 α ,2 α (Z),4 α]-1H-indole-5-sulfonamide;
- 10 (Z)-7-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6,7-dihydro-6-oxo-5H-1,3-dioxolo[4,5-f]indole-5-carboxamide;
- (E)-7-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6,7-dihydro-6-oxo-5H-1,3-dioxolo[4,5-f]indole-5-carboxamide;
- 15 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-methyl-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;
- 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,5-dimethyl-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;
- 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-methyl-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;
- 20 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-pyrrolo[3,2-b]pyridin-2-one;
- 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one;
- 25 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one; and
- 3-1-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]ethylidene]-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one.

The present invention also relates to a pharmaceutical composition for treating

30 a condition selected from the group consisting of acquired immunodeficiency syndrome ("AIDS"), asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising an amount of a

compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating a condition selected from the group consisting of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating such condition.

The present invention also relates to a pharmaceutical composition for inhibiting the effects of phosphodiesterase type IV in a mammal, including a human, comprising a phosphodiesterase type IV inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of inhibiting the effects of phosphodiesterase type IV in a mammal, including a human, comprising administering to said mammal a phosphodiesterase type IV inhibiting amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating a condition selected from the group consisting of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in inhibiting the action of phosphodiesterase type IV, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating a condition selected from the group consisting of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in inhibiting the action of phosphodiesterase type IV.

The present invention also relates to a pharmaceutical composition for treating a disorder in a mammal, including a human, the treatment of which is effected or facilitated by blocking the action of phosphodiesterase type IV, comprising an amount

-10-

of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating a disorder in a mammal, including a human, the treatment of which is effected or facilitated by blocking the action of phosphodiesterase type IV, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating such disorder.

Some of the compounds of the present invention have chiral centers and therefore exist in different enantiomeric forms. For example, when the broken line represents a single bond and R^9 is not hydrogen, the compound can exist in at least four enantiomeric forms. Some of the compounds of the present invention can also exist in different regioisomeric forms. For example, when the broken line represents a double bond, both the E and Z isomers can be isolated. This invention relates to all optical isomers, all stereoisomers, and all regioisomers of compounds of formula I, and mixtures thereof.

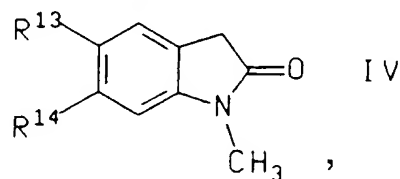
Formula I above includes compounds identical to those depicted but for the fact that one or more hydrogen or carbon atoms are replaced by radioactive isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism studies, pharmacokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area include studies of selective inhibition of phosphodiesterase type IV in vivo binding in the relevant tissues for asthma, e.g., immune or inflammatory type cells that are directly or indirectly involved in inflammation, and the like.

Also within the scope of this invention are the pharmaceutically acceptable salts of the compounds of the formula I where acidic or basic functionalities are incorporated as substituents. The pharmaceutically acceptable acid salts are those formed from acids which form non-toxic acid salts, for example, hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, acid phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate and formate salts. Pharmaceutically acceptable cationic salts include those non-toxic salts based on alkali and alkaline earth metals, for example, sodium, lithium, potassium, calcium and magnesium, as well as non-toxic ammonium,

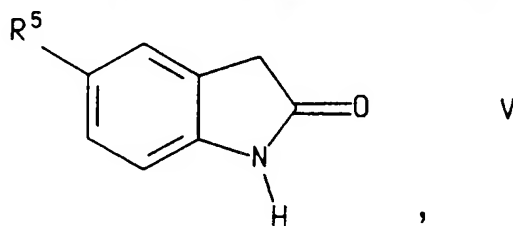
-11-

quaternary ammonium and amine cations, for example, ammonium, tetramethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, N,N'-dibenzylethylenediamine, N-methylglucamine, meglumine, ethanolamine and diethanolamine.

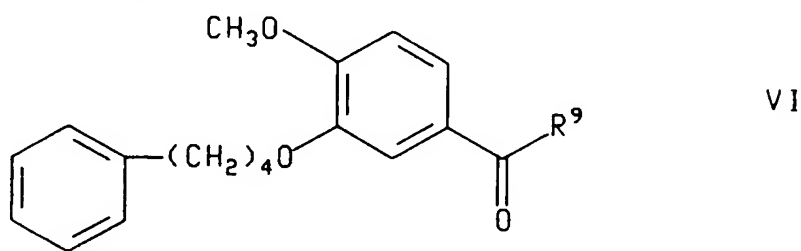
5 The present invention also relates to the following intermediates used in the preparation of compounds of formula I:



wherein R^{13} and R^{14} are independently selected from hydrogen and methoxy;



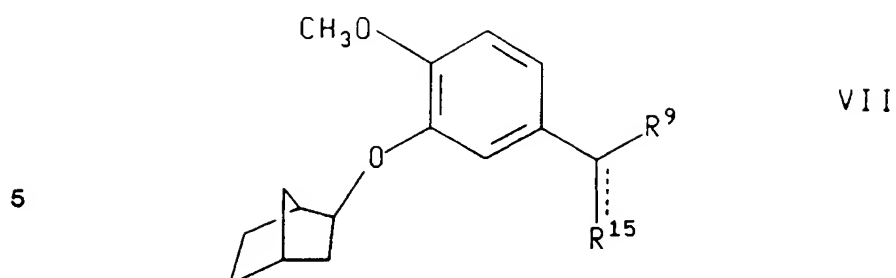
wherein R^5 is $\text{SO}_2\text{NR}^8\text{R}^{12}$;



wherein R^9 is hydrogen or $(\text{C}_1\text{-C}_6)$ alkyl; and

30

-12-



wherein R^9 is hydrogen or (C₁-C₈) alkyl, R^{15} is oxygen or hydroxy, and the broken line represents a double bond when R^{15} is oxygen.

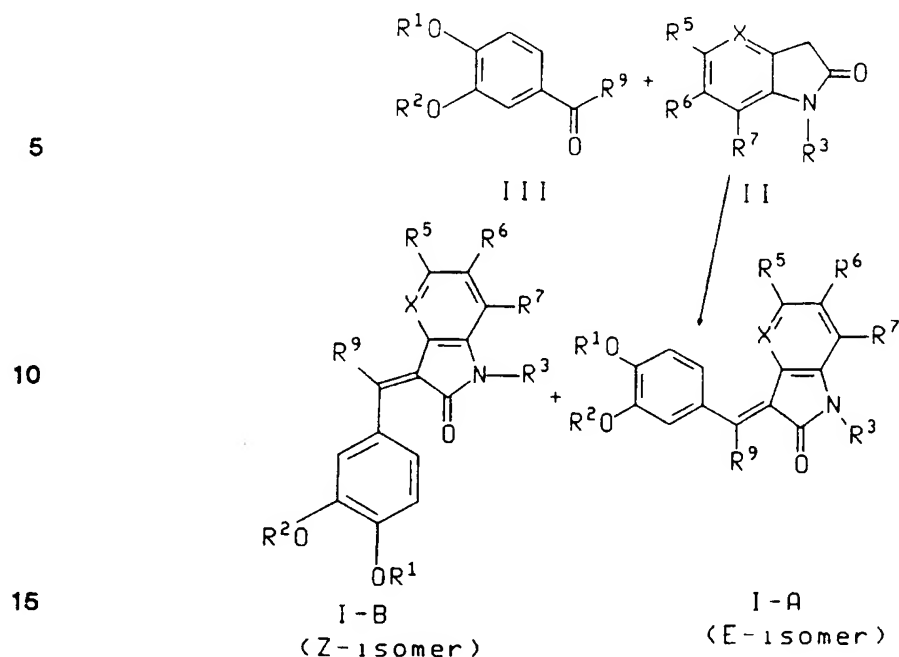
10

Detailed Description of the Invention

The compounds of formula I may be prepared as described in the following reaction schemes and discussion. Unless otherwise indicated, X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , the broken lines, and the wavy lines in the reaction schemes and discussion that follow are defined as above.

-13-

Scheme 1



With reference to reaction Scheme 1, the compounds of the present invention wherein the broken line of formula I represents a double bond (Formulae I-A and I-B), may be prepared by an Aldol condensation, using conditions well known to those skilled in the art. Thus, a compound of formula II is reacted with a compound of formula III, preferably under an inert atmosphere in a reaction inert solvent such as water, methanol, ethanol, butanol, isopropanol, acetone, ether, chloroform, methylene chloride, dioxane, tetrahydrofuran, or dimethoxyethane. To this mixture is added a base such as pyrrolidine, piperidine, diethylamine, triethylamine, Hunig's base, aqueous sodium hydroxide, barium hydroxide, aluminum t-butoxide, sodium ethoxide, potassium hydroxide, morpholine, methyl lithium, butyl lithium, sodium hydride, or pyridine. The actual base utilized will depend somewhat upon the solvent utilized. The reaction mixture is stirred for 2 to 72 hours at a temperature of between 0° and 140°. When the reaction is complete, the compounds of formula I-A (the E isomer) and formula I-B (the Z isomer) are isolated via methods well known to those skilled in the art.

The compounds of formula I-A, wherein R³=hydrogen, can be alkylated to form compounds of formula I-A, wherein R³=(C₁-C₆) alkyl, using reaction conditions well

-14-

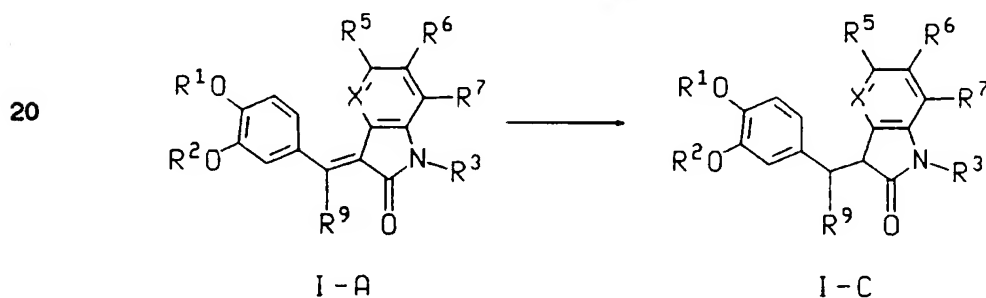
known to one skilled in the art. These reaction conditions can also be performed on compounds of formula I-B, wherein R^3 =hydrogen, and on compounds of formula II, wherein R^3 =hydrogen, to effect analogous transformations (and to yield, among other compounds, the compounds of formula IV). Thus, a compound of formula I-A wherein

5 R^3 is hydrogen can be combined with a base such as potassium carbonate, sodium hydride, sodium carbonate, sodium hydroxide, potassium hydroxide, potassium *t*-butoxide, butyl lithium, and potassium fluoride. The mole ratio of starting material oxindole to base will preferably be from about 1.0 to about 0.5. These compounds can be combined in a suitable solvent such as acetone, chloroform, methylene chloride,

10 dimethylformamide, ethanol, butanol, isopropanol, dimethylsulfoxide, or a mixture of two or more of the foregoing solvents. To this mixture, an alkylating agent, such as an alkyl halide or alkyl sulfate, can be added. The reaction can be stirred for a time period from about two to about 72 hours, at a temperature between 0° and 100°C. Additional reagents, such as phase transfer catalysts, can be added. When the reaction is

15 complete, the compounds of formula I-A can be isolated via methods well known to one skilled in the art.

Scheme 2



25

With reference to reaction Scheme 2, the compounds of the present invention wherein the broken line of formula I represents a single bond (formula I-C) can be prepared by a hydrogenation reaction, using reaction conditions well known to one skilled in the art. These reaction conditions can also be performed on compounds of

30 formula I-B to effect analogous transformations. Thus, a compound of formula I-A can be dissolved in a solvent such as ethyl acetate, tetrahydrofuran, methanol, ethanol, butanol, isopropanol, ether, dioxane, chloroform, methylene chloride, dimethoxyethane, or a combination thereof. The mixture can be combined with a catalyst such as

palladium, rhodium, Raney nickel, platinum, platinum oxide, palladium hydroxide, nickel boride, ruthenium, zinc oxide, chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst), or pentacyanocobaltate(II), and shaken under a hydrogen atmosphere for about two to about 72 hours at a pressure of about atmospheric to about 100 atm., at
5 a temperature between 0° and 250°. When the reaction is complete, the compounds of formula I-C can be isolated via methods well known to those skilled in the art. Other possible reducing agents to effect this transformation can be used such as sodium, lithium, chromous ion, zinc sodium hydrophosphate and palladium, trifluoroacetic acid and triethylsilane, hydrazine with an oxidizing agent under reaction conditions well
10 known to one skilled in the art.

The compounds of formula I-A, wherein R^3 =hydrogen, can also be acylated to form compounds of formula I-A, wherein R^3 =(C₁-C₆) alkoxy carbonyl, using reaction conditions well known to those skilled in the art. These reaction conditions can also be performed on compounds of formula I-B, wherein R^3 =hydrogen, and on compounds
15 of formula II, wherein R^3 =hydrogen, to effect analogous transformations. Thus, a compound of formula I-A wherein R^3 =hydrogen can be combined with an appropriate acylating agent (such as ethyl chloroformate). In the case of liquid acylating agents, this reagent can also be used as the solvent for the reaction. If, however, the acylating agent is not a liquid, then the solvent for the reaction could be solvents such as
20 dimethylformamide, ethanol, butanol, isopropanol, dimethylsulfoxide, chloroform, or methylene chloride. A base is then added to the reaction mixture; suitable bases include but are not limited to potassium carbonate, sodium hydride, sodium carbonate, sodium hydroxide, potassium hydroxide, potassium t-butoxide, butyl lithium, potassium fluoride, and sodium. Phase transfer catalysts can also be added, if appropriate. The
25 reaction can be stirred at a temperature between 0° and 150°C, for a period of time from about three to about 72 hours. When the reaction is complete, the compounds of formula I-A can be isolated via methods well known to those skilled in the art.

The compounds of formula I-A, wherein R^4 , R^5 , R^6 and/or R^7 =hydroxy, can also be acylated to form compounds of formula I-A, wherein R^4 , R^5 , R^6 , and/or R^7 =(C₂-C₆)
30 acyloxy, using reaction conditions well known to those skilled in the art. These reaction conditions can also be performed on compounds of formula I-B, wherein R^4 , R^5 , R^6 , and/or R^7 =hydroxy, and on compounds of formula II wherein R^4 , R^5 , R^6 and/or R^7 =hydroxy, to effect analogous transformations. Thus, a compound of formula I-A

-16-

wherein R^4 , R^5 , R^6 , and/or R^7 =hydroxy, can be combined with a base such as aqueous sodium hydroxide, piperidine, diethylamine, triethylamine, Hunig's base, barium hydroxide, aluminum *t*-butoxide, sodium ethoxide, potassium hydroxide, morpholine, methyl lithium, butyl lithium, sodium hydride, pyridine, mercury oxide or potassium carbonate in a solvent such as water, methanol, ethanol, butanol, isopropanol, acetone, ether, dioxane, chloroform, methylene chloride, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, dimethylformamide, or a mixture of two or more of the foregoing solvents, depending on the choice of base. The resulting mixture can be stirred at a temperature between 0° and 150°C. An acylating agent can then be added to this mixture, such as acyl anhydride or acyl halide. The reaction can be stirred for about one-half to about 72 hours. Phase transfer catalysts can be added, if appropriate. When the reaction is complete, the compounds of formula I-A can be isolated via methods well known to those skilled in the art.

The compounds of formula I-A, wherein R^4 , R^5 , R^6 , and/or R^7 =hydroxy, can also be alkylated to form compounds of formula I-A, wherein R^4 , R^5 , R^6 , and/or R^7 =(C_1 - C_8) alkoxy, (C_3 - C_7) cycloalkoxy, phenyl-(C_1 - C_8)alkoxy, or (C_6 - C_{12}) polycycloalkoxy, using reaction conditions well known to those skilled in the art. These reaction conditions can also be performed on compounds of formula I-B, wherein R^4 , R^5 , R^6 , and/or R^7 =hydroxy, and on compounds of formula II, wherein R^4 , R^5 , R^6 , and/or R^7 =hydroxy, as well as on compounds of formula III wherein R^1 and/or R^2 =hydroxy, to effect analogous transformations (and to yield, among other compounds, the compounds of formula VI). Thus, a compound of formula I-A wherein R^4 , R^5 , R^6 , and/or R^7 =hydroxy, can be dissolved in a reaction inert solvent such as acetone, ether, chloroform, methylene chloride, dioxane, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, dimethylformamide, or a mixture of two or more of the foregoing solvents. To this mixture is added a base such as aqueous sodium hydroxide, barium hydroxide, aluminum *t*-butoxide, sodium methoxide, sodium ethoxide, potassium hydroxide, potassium carbonate, methyl lithium, butyl lithium, sodium hydride, silver oxide, potassium fluoride, or tetraethylammonium fluoride. The choice of base may depend somewhat on the choice of solvent. The reaction mixture can be stirred for about one-half hour to about 3 hours, at a temperature between -78°C and room temperature. Upon formation of the alkoxide, the alkylating agent such as an alkyl halide, or alkyl sulfate is added. Additional reagents can be added, such as

hexamethylphosphoramide, potassium iodide, sodium iodide, or phase transfer catalysts. The reaction mixture is then stirred for one to 24 hours, at a temperature between -20°C and 150°C. When the reaction is complete, the compounds of the formula I-A can be isolated via methods well known to those skilled in the art.

5 Alternatively, this transformation could be carried out under the following reaction conditions. A compound of formula I-A wherein R⁴, R⁵, R⁶, and/or R⁷=hydroxy, can be dissolved in a reaction inert solvent such as ether, chloroform, methylene chloride, dioxane, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, dimethylformamide, or a mixture of two or more of the foregoing solvents. The
10 alkylation is then performed using an alkylating agent such as an alkyl alcohol, in combination with a triarylphosphine or trialkyl phosphine, and a dialkylazodicarboxylate. The reaction mixture can be stirred for about 2 to about 150 hours, at a temperature between 0° and 150°C. When the reaction is complete, the compounds of formula I-A can be isolated via methods well known to those skilled in the art.

15 The compounds of formula I-A, wherein R³=hydrogen, can also be alkylated to form compounds of formula I-A wherein R³=(C₁-C₆) alkoxycarbonyl-(C₁-C₆) alkyl, using reaction conditions well known to one skilled in the art. These reaction conditions can also be performed on compounds of formula I-B, wherein R³=hydrogen, and on compounds of formula II, wherein R³=hydrogen, to effect analogous transformations.
20 Thus, a compound of formula I-A wherein R³ is hydrogen can be dissolved with an alkoxycarbonyl alkylating agent such as ethyl chloroacetate in a solvent such as dimethylformamide, acetone, ether, chloroform, methylene chloride, dioxane, tetrahydrofuran, dimethoxy ethane, dimethylsulfoxide, or a mixture of two or more of the foregoing solvents. The reaction can be cooled, and then a base can be added such
25 as sodium hydride, aqueous sodium hydroxide, barium hydroxide, aluminum t-butoxide, sodium methoxide, sodium ethoxide, potassium hydroxide, potassium carbonate, methyl lithium, butyl lithium, silver oxide, potassium fluoride, or tetraethylammonium fluoride. The reaction can then be stirred for about 10 minutes to 72 hours, at a temperature between -20° and 150°C. Additional reagents can be added such as
30 hexamethylphosphoramide, potassium iodide, or sodium iodide. When the reaction is complete, the compounds of formula I-A can be isolated via methods well known to those skilled in the art.

-18-

The compounds of formula I-A, wherein R^4 , R^5 , R^6 , and/or R^7 =nitro, can also be reduced to form compounds of formula I-A, wherein R^4 , R^5 , R^6 , and/or R^7 =amino, using reaction conditions well known to those skilled in the art. These reactions can also be performed on compounds of formula I-B, wherein R^4 , R^5 , R^6 , and/or R^7 =nitro, and on

5 compounds of formula II, wherein R^4 , R^5 , R^6 , and/or R^7 =nitro, to effect analogous transformations. Thus, a compound of formula I-A wherein R^4 , R^5 , R^6 , and/or R^7 =nitro, can be combined with a reducing agent in a solvent such as water, methanol, ethanol, butanol, isopropanol, acetone, ether, dioxane, chloroform, methylene chloride, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, dimethylformamide, or a mixture

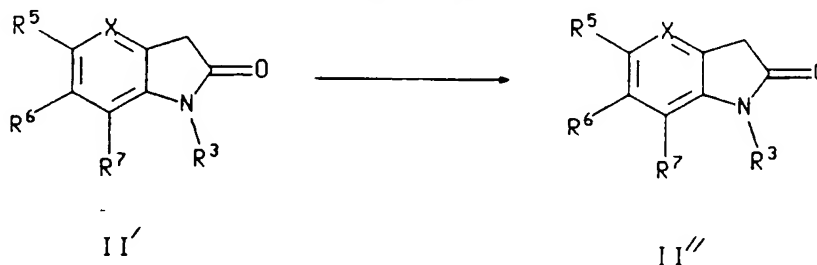
10 of two or more of the foregoing solvents. Examples of reducing agents are iron powder, zinc, tin, hydrogen chloride, acetic acid, formic acid, sulfuric acid, catalytic hydrogenation, titanium trichloride, sodium sulfide, ammonium sulfide, polysulfides, sodium dihydro(trithio)borate, sodium borohydride with nickel chloride or cobalt chloride, or hydrazine with a catalyst (e.g. palladium on carbon). The mixture can be

15 stirred at a temperature between 0° and 200°C , for a time period of from about one half to about 72 hours. When the reaction is complete, the compounds of formula I-A can be isolated via methods well known to those skilled in the art.

Reaction schemes 3 and 4 illustrate the preparation of intermediates of the present invention.

20

Scheme 3



25

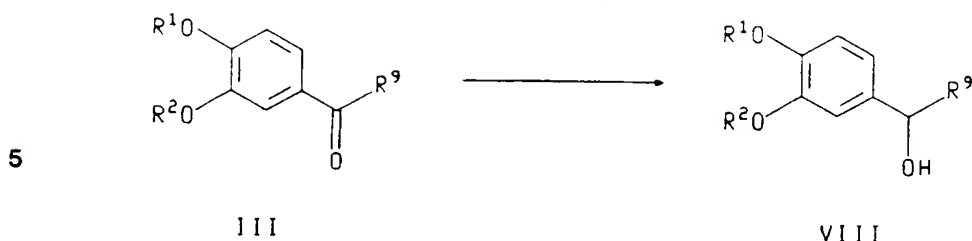
With reference to reaction Scheme 3, the compounds of formula II', wherein R^4 , R^5 , R^6 , and/or R^7 =hydrogen, can also be alkylated, acylated, or sulfonylated to form

30 compounds of formula II'', wherein R^4 , R^5 , R^6 , and/or R^7 =(C_1 - C_6) alkyl, (C_1 - C_6) alkylcarbonyl, or $\text{SO}_2\text{NR}^8\text{R}^{12}$ (of which the compounds of formula V are an example), using reaction conditions well known to those skilled in the art. Thus, to a suspension of a Lewis acid such as aluminum chloride, boron trifluoride, zinc chloride, gallium

chloride, ferric chloride, or tin chloride, in a solvent such as carbon disulfide, acetone, ether, chloroform, methylene chloride, dioxane, tetrahydrofuran, dimethoxyethane, nitrobenzene, acetic acid, or a mixture of two or more of the foregoing solvents, was added an alkyl halide, such as ethyl chloride, an acyl halide, such as acetyl chloride, or a substituted sulfonyl halide, such as dimethylsulfonyl chloride. This is followed by addition of a compound of formula II' wherein R⁴, R⁵, R⁶, and/or R⁷=hydrogen. The reaction can be stirred at a temperature between 0° and 250°C, for a period of time from about 2 to about 72 hours. When the reaction is complete, the compounds of formula II'' can be isolated via methods well known to those skilled in the art. The compounds of formula II' are generally commercially available or are known to those skilled in the art.

-20-

Scheme 4



With reference to reaction Scheme 4, the compounds of formula III, wherein R^9 =hydrogen, can be reacted to form compounds of formula VIII, wherein R^9 =(C_1 - C_6) alkyl (of which the compounds of formula VII are an example), using reaction conditions well known to those skilled in the art. Thus, a compound of formula III wherein R^9 is H can be dissolved in a solvent such as ether, dioxane, tetrahydrofuran, dimethoxyethane, hexane, pentane, or a mixture of two or more of the foregoing solvents. The reaction mixture can be cooled to a temperature between -100° and 20°C , and then a suitable organometallic reagent can be added such as organomagnesium halide, organolithium, organocuprate, organozinc, organotitanium, organozirconium, or organomanganese. Other additives can also be utilized, such as hexamethylphosphoramide, N,N,N',N'-tetramethylenediamine, amino alcohol, titanium halide, zirconium halide, dibromoethane, iodine, or combinations thereof. The reaction can be stirred for a period of time of from about one half to about 150 hours, at a temperature between 0°C and 150°C . When the reaction is complete, compounds of formula VIII can be isolated via methods well known to those skilled in the art. The compounds of formula III are generally commercially available or known to those skilled in the art.

25 The compounds of formula VIII, wherein R^9 =(C_1 - C_6) alkyl, can be oxidized to form compounds of formula III, wherein R^9 =(C_1 - C_6) alkyl, using reaction conditions well known to those skilled in the art. Thus, a compound of formula VIII can be combined with a solvent such as water, acetone, acetic acid, trifluoroacetic acid, dimethylformamide, dimethylsulfoxide, ether, dioxane, tetrahydrofuran, dimethoxyethane, hexane, pentane, pyridine, chloroform, methylene chloride, benzene, or a mixture of two or more of the foregoing solvents, and the mixture can be cooled to a temperature between -20° and 15°C . An oxidizing reagent can then be added, such as acid dichromate, potassium permanganate, bromine, manganese dioxide,

30

5 ruthenium tetroxide, Jones reagent (chromic acid and sulfuric acid in water), Collin's reagent (dipyridine chromium (VI) oxide), pyridinium chlorochromate, pyridinium dichromate, sodium hypochlorite, dimethyl sulfoxide, tetrapropylammonium permuthenate, ceric ammonium nitrate, silver carbonate, hydrogen peroxide, Fremy's salt, m-chloroperbenzoic acid, aluminum t-butoxide, N-halosuccinimide, dicyclohexylcarbodiimide, or chromium trioxide. The mixture can then be allowed to warm to about room temperature and then stirred for about one half to about 150 hours. Additional additives can be utilized, such as hexamethylphosphoramide, phase transfer catalysts, or tetrabutylammonium iodide. When the reaction is complete, the
10 compounds of the formula III can be isolated via methods well known to those skilled in the art.

The preparation of other compounds of the present invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in
15 the art.

In each of the reactions discussed or illustrated above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e. about 1 atmosphere, is preferred as a matter of convenience.

20 The novel compounds of the formula I and their pharmaceutically acceptable salts (hereinafter referred to, collectively, as "the active compounds of the present invention") are useful as selective inhibitors of phosphodiesterase type IV, i.e., they possess the ability to inhibit the effects of phosphodiesterase type IV in mammals, and therefore they are able to function as therapeutic agents in the treatment of the
25 aforementioned disorders and diseases in an afflicted mammal.

Those compounds of the present invention which are basic in nature (such as those compounds of formula I, wherein R^4 , R^5 , R^6 , and/or $R^7=NR^8R^{12}$) are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals,
30 it is often desirable in practice to initially isolate a compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid

-22-

addition salt. The acid addition salts of the basic compounds of this invention are readily prepared by treating the basic compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. Pharmaceutically-acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with hydrochloric acid (HCl), hydrobromic acid (HBr), nitric acid (HNO₃), sulfuric acid (H₂SO₄), phosphoric acid (H₃PO₄), methanesulfonic acid (CH₃SO₃H), toluenesulfonic acid (p-CH₃C₆H₄SO₃H), acetic acid (CH₃CO₂H), gluconic acid, tartaric acid, maleic acid and succinic acid. Those compounds of the present invention which are acidic in nature are capable of forming a wide variety of different salts with various inorganic and organic bases. Pharmaceutically-acceptable cationic salts of the compounds of this invention include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine and diethanolamine.

The compounds of the present invention and their pharmaceutically acceptable salts are believed to exhibit phosphodiesterase type IV receptor-binding activity and therefore are of value in the treatment of a wide variety of clinical conditions the treatment of which are effected or facilitated by a decrease in phosphodiesterase type IV mediated activity. Such conditions include AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases. Hence, these compounds are readily adapted to therapeutic use as selective inhibitors of phosphodiesterase type IV for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the present invention are readily adapted to clinical use as selective inhibitors of phosphodiesterase type IV. The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit phosphodiesterase type IV may be shown by the following Human Lung *in vitro* assay.

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at

-23-

4°C. The supernatant is filtered twice through a 0.22 μ m filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise sodium chloride gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE IV activity, determined by [3 H]cAMP hydrolysis and the ability of a known PDE IV inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in dimethylsulfoxide (DMSO) at a concentration of 10 mM and diluted 1:25 in water (400 μ M compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. Final DMSO concentration in assay tube is 1%. In duplicate the following are added, in order, to a 12 X 75 mm glass tube (all concentrations are given as final concentrations in assay tube).

- i) 25 μ l compound or DMSO (1%, for control and blank)
- ii) 25 μ l pH 7.5 Tris buffer
- iii) [3 H]cAMP (1 μ M)
- iv) 25 μ l PDE IV enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [3 H]cAMP is washed with 2 x 6 ml washing buffer, and [3 H]5AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [3 H].

$$\% \text{ Inhibition} = 1 - \frac{\text{average cpm (test compound)} - \text{average cpm (blank)}}{\text{average cpm (control)} - \text{average cpm (blank)}}$$

IC₅₀ is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [³H]cAMP to [³H]5'AMP.

For treatment of the various conditions described above, the compounds of the invention and their pharmaceutically acceptable salts can be administered to the patient
5 either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition according to standard pharmaceutical practice. Such administration may be carried out in single or multiple doses. A compound can be administered via a variety of conventional routes of administration including orally, parenterally, by inhalation, and topically. When the compounds are
10 administered orally, the dose range will generally be from about 0.1 to about 500 mg/day for an average adult patient (70 kg), preferably from about 7 to about 70 mg/day in single or divided doses. If parenteral administration is desired, then an effective dose will generally be from about 0.1 to about 70 mg/day. For intranasal or inhaler administration, the dosage will generally be formulated as a 0.1 to 1% (w/v)
15 solution. In some instances it may be necessary to use dosages outside these limits, since the dosage will necessarily vary according to the species, age, weight, and response of the individual patient, severity of the patient's symptoms, potency of the particular compound being administered, type of pharmaceutical formulation chosen, and time period and interval at which administration is carried out.

20 The compounds of the invention and their pharmaceutically acceptable salts can be administered in a wide variety of different dosage forms, such as in the form of tablets, powders, lozenges, troches, hard candies, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, syrups or capsules, aqueous solutions or suspensions, injectable solutions, elixirs, and the like. Such carriers
25 include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. In general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as
30 microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia.

Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the compounds of the present invention topically and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The present invention is illustrated by the following Examples and Preparations. It will be understood, however, that the invention is not limited to the specific details of these Examples and Preparations. All melting points are uncorrected. In the procedures and tables that follow, "stchm" means stereochemistry, "Ex." means Example, "mp(°C)" means melting point in degrees Celcius, "MF" means molecular formula, "Anal." means elemental analysis, "Calc" means calculated, "m/z" means mass to charge ratio, "H" means hydrogen, "C" means carbon, "O" means oxygen, "Me" means methyl, "Et" means ethyl, "Br" means bromine, and "Cl" means chlorine.

EXAMPLESEXAMPLES 1 AND 2

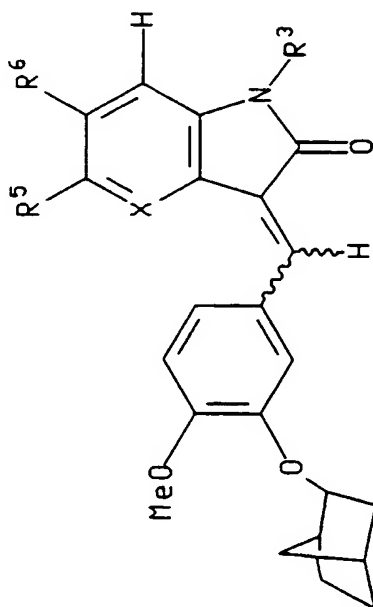
3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one (Example 1) and 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one (Example 2)

3-(exo-Bicyclo [2.2.1] hept-2-yloxy)-4-methoxybenzaldehyde (677 mg, 2.75 mmol; disclosed in WO 87/06576 published November 5, 1987), and 5-chloro-1-methyloxindole (500 mg, 2.75 mmol; Chemical Abstracts registry number 41192-33-0, were dissolved in 10 ml of methanol under an inert atmosphere. To this brown, homogeneous mixture was added 0.23 ml of pyrrolidine (2.75 mmol) via syringe. The reaction mixture was stirred at room temperature for ten hours. The solvent was then stripped off and the resulting yellow oil was purified via flash chromatography (1:1 ethyl ether/hexane) to provide the desired Z-adduct 3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one (125 mg, 11% yield) as a yellow solid (Example 1): m.p. 149-151°. Analysis calculated for C₂₄H₂₄ClNO₃: C, 70.32; H, 5.90; N, 3.42. Found: C, 70.26; H, 5.87; N, 3.38. The corresponding E-adduct 3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one (Example 2) was also obtained in 6% yield, m.p. 142-144°C. Analysis calculated for C₂₄H₂₄ClNO₃: C, 70.32; H, 5.90; N, 3.42. Found: C, 70.34; H, 5.85; N, 3.36.

-27-

EXAMPLES 3-41

Following the method of Example 1, the following products were prepared by reacting 3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxy benzaldehyde with an appropriate oxindole (as determined by R⁵ and R⁶ indicated below) in place of the 5-chloro-1-methyloxindole. Unless otherwise indicated, the starting material oxindole is either known in the literature or is commercially available. The wavy lines indicate that the following compounds can exist as either the E or Z stereoisomers:



10

15

20

Ex.	R ³	R ⁵	R ⁶	X	Stichm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
3	H	H	H	C-H	E	204-205	C ₂₃ H ₂₃ NO ₃	Calc: Found:	76.43 76.24	6.41 6.35	3.88 3.88		

25

Ex.	R'	R ^o	R ^o	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
4	H	H	H	C-H	Z	186-187	C ₂₃ H ₂₃ NO ₃ • 1/4H ₂ O	Calc: Found:	75.49 75.84	6.47 6.17	3.83 3.81	C ₂₃ H ₂₃ NO ₃	Calc: 361.1678 Found: 361.17835
5	Me	H	H	C-H	E	80-110	C ₂₄ H ₂₈ NO ₃ • 1/2H ₂ O	Calc: Found:	74.98 75.35	6.82 6.46	3.64 3.66	C ₂₄ H ₂₈ NO ₃	Calc: 375.1834 Found: 375.1830
6	Me	H	H	C-H	Z	116-117	C ₂₄ H ₂₈ NO ₃	Calc: Found:	76.78 76.68	6.71 6.55	3.73 3.71		
7	Et	H	H	C-H	E	143-144	C ₂₈ H ₃₇ NO ₃	Calc: Found:	77.09 77.05	6.99 7.07	3.60 3.59		
8	Et	H	H	C-H	Z	foam	C ₂₈ H ₃₇ NO ₃ • 1/2H ₂ O	Calc: Found:	76.35 75.75	7.08 7.12	3.51 3.78	C ₂₈ H ₃₇ NO ₃	Calc: 389.1991 Found: 389.1970
9	H	OH	H	C-H	E	145-157	C ₂₃ H ₂₃ NO ₄ • 3/4H ₂ O	Calc: Found:	70.66 70.55	6.32 6.10	3.58 3.53	C ₂₃ H ₂₃ NO ₄	Calc: 377.1627 Found: 377.1606
10	H	OH	H	C-H	Z	162-164	C ₂₃ H ₂₃ NO ₄ • 1/2H ₂ O	Calc: Found:	71.49 71.88	6.26 5.92	3.62 3.76	C ₂₃ H ₂₃ NO ₄	Calc: 377.1627 Found: 377.1620
11	Et	OH	H	C-H	Z	212-213	C ₂₈ H ₃₇ NO ₄ • 1/4H ₂ O	Calc: Found:	73.24 72.97	6.76 6.76	3.42 3.42	C ₂₈ H ₃₇ NO ₄	Calc: 405.1940 Found: 405.18512

-29-

Ex.	R ³	R ²	R ¹	R ⁰	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
12	H	H	OMe	C-H	Z		187-189	C ₂₄ H ₂₈ NO ₄ • 1/4H ₂ O	Calc: Found:	72.80 72.72	6.49 6.34	3.54 3.55	C ₂₄ H ₂₈ NO ₄	Calc: 391.1784 Found: 391.17407
13	CONH ₂	OCH ₂ O (R ² and R ¹ con- nected)	see R ¹	C-H	E		191-193						C ₂₈ H ₃₄ N ₂ O ₆	Calc: 448.1634 Found: 448.16474
14	CONH ₂	OCH ₂ O (R ² and R ¹ con- nected)	see R ¹	C-H	Z		189-191	C ₂₈ H ₃₄ N ₂ O ₆	Calc: Found:	66.95 67.07	5.39 5.01	6.25 6.30	C ₂₈ H ₃₄ N ₂ O ₆	Calc: 448.1634 Found: 448.16789
15	H	Br	H	C-H	E		212-213	C ₂₃ H ₂₂ BrNO ₃	Calc: Found:	62.74 62.47	5.04 4.88	3.18 3.27		
16	H	Br	H	C-H	Z		178-179	C ₂₃ H ₂₂ BrNO ₃	Calc: Found:	62.74 62.48	5.04 4.90	3.18 3.08		
17	H	Cl	H	C-H	E		229-230	C ₂₃ H ₂₂ ClNO ₃	Calc: Found:	69.78 69.80	5.60 5.48	3.54 3.48		
18	H	Cl	H	C-H	Z		191-192	C ₂₃ H ₂₂ ClNO ₃	Calc: Found:	69.78 69.45	5.60 5.55	3.54 3.53		
19	CONH ₂	Cl	H	C-H	E		209-211	C ₂₄ H ₂₃ ClN ₂ O 4	Calc: Found:	65.68 65.37	5.28 5.27	6.38 6.25		
20	CONH ₂	Cl	H	C-H	Z		198-200	C ₂₄ H ₂₃ ClN ₂ O 4	Calc: Found:	65.68 65.97	5.28 5.12	6.38 6.16		
21	H	H	Cl	C-H	E		243-245	C ₂₃ H ₂₂ ClNO ₃	Calc: Found:	69.78 69.49	5.60 5.47	3.54 3.50		

5

10

-30-

Ex.	R ³	R ²	R ¹	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
22	H	H	Cl	C-H	Z	184-186	C ₂₃ H ₂₂ ClNO ₃ • 1/4H ₂ O	Calc: Found:	68.99 68.86	5.66 5.51	3.50 3.52	C ₂₃ H ₂₂ ClN O ₃	Calc: 395.1288 Found: 395.1287
23	OMe	H	Cl	C-H	E	123-126	C ₂₄ H ₂₄ ClNO ₄	Calc: Found:	67.68 67.33	5.68 5.58	3.29 3.35		
24	OMe	H	Cl	C-H	Z	131-133						C ₂₄ H ₂₄ ClN O ₄	Calc: 425.1394 Found: 425.1396
25	H	NO ₂	H	C-H	E	270-272	C ₂₃ H ₂₂ N ₃ O ₆ • 1/2H ₂ O	Calc: Found:	66.50 66.38	5.58 5.24	6.74 6.84	C ₂₃ H ₂₂ N ₃ O ₆	Calc: 406.1529 Found: 406.1505
26	H	NO ₂	H	C-H	Z	203-206	C ₂₃ H ₂₂ N ₃ O ₆	Calc: Found:	67.97 67.73	5.46 5.16	6.89 6.82		
27	H	NO ₂	H	C-H	E	317-321	C ₂₃ H ₂₁ N ₃ O ₇ • 1/4H ₂ O	Calc: Found:	60.59 60.55	4.75 4.57	9.22 8.98	C ₂₃ H ₂₁ N ₃ O ₇	Calc: 451.1380 Found: 451.1387
28	H	Cl	H	N	E	246-247	C ₂₂ H ₂₁ ClN ₂ O ;	Calc: Found:	66.58 66.28	5.33 5.08	7.06 7.43		
29	H	H	H	N	E	187-188	C ₂₂ H ₂₂ N ₃ O ₃ • 1/8H ₂ O	Calc: Found:	72.46 72.40	6.15 6.04	7.68 7.62	C ₂₂ H ₂₂ N ₃ O ₃	Calc: 362.1630 Found: 362.16102

- 31 -

Ex.	R ³	R ²	R ¹	R ⁰	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
30	H	Me	H	C-H	E		199-200						C ₂₄ H ₂₈ NO ₃	Calc: 375.1834 Found: 375.1863
31	H	Me	H	C-H	Z		135-141	C ₂₄ H ₂₈ NO ₃	Calc: Found:	76.78 76.47	6.71 6.72	3.73 3.56		
32	H	COMe	H	C-H	E		200-202	C ₂₈ H ₂₈ NO ₄ • 1/2H ₂ O	Calc: Found:	72.80 73.03	6.35 6.33	3.40 3.33	C ₂₈ H ₂₈ NO ₄	Calc: 403.1784 Found: 403.1778
33	H	COMe	H	C-H	Z		128-132	C ₂₈ H ₂₈ NO ₄ • 1/2H ₂ O	Calc: Found:	72.80 73.15	6.35 6.42	3.40 3.50	C ₂₈ H ₂₈ NO ₄	Calc: 403.1784 Found: 403.1814
34	Me	OMe	H	C-H	E		119-121	C ₂₈ H ₂₇ NO ₄ • 1/8H ₂ O	Calc: Found:	73.64 73.31	6.74 6.36	3.44 3.24	C ₂₈ H ₂₇ NO ₄	Calc: 405.1940 Found: 405.1920
35	Me	OMe	H	C-H	Z		foam	C ₂₈ H ₂₇ NO ₄	Calc: Found:	74.05 73.80	6.71 6.88	3.45 3.15		
36	Me	H	OMe	C-H	E		154-156						C ₂₈ H ₂₇ NO ₄	Calc: 405.1940 Found: 405.19276
37	Me	H	OMe	C-H	Z		111.5- 113	C ₂₈ H ₂₇ NO ₄	Calc: Found:	74.05 74.10	6.71 6.69	3.45 3.47		

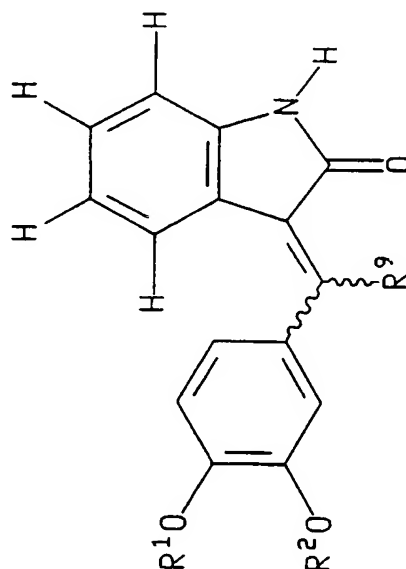
- 32 -

Ex.	R ³	R ⁵	R ⁶	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
38	Me	OMe	OMe	C-H	E	186-187	C ₂₈ H ₂₈ NO ₆ • 1/4H ₂ O	Calc: Found:	70.97 70.82	6.76 6.58	3.18 3.11	C ₂₈ H ₂₈ NO ₆	Calc: 435.2046 Found: 435.20705
39	Me	OMe	OMe	C-H	Z	123-125	C ₂₈ H ₂₈ NO ₆	Calc: Found:	71.71 71.49	6.71 6.65	3.22 3.29		
40	H	SO ₂ NMe ₂	H	C-H	E	253-254	C ₂₈ H ₂₈ N ₂ O ₆ S	Calc: Found:	64.08 63.92	6.02 5.78	5.98 5.78		
41	H	SO ₂ NMe ₂	H	C-H	Z	180-200	C ₂₈ H ₂₈ N ₂ O ₆ S • 1/2H ₂ O	Calc: Found:	62.88 62.88	6.12 6.07	5.87 5.82	C ₂₈ H ₂₈ N ₂ O ₆ S	Calc: 468.1719 Found: 468.1698


R⁷ in Example 27 is NO₂. The starting material oxindole for Examples 34 and 35 is prepared in PREPARATION A, *infra*. The starting material oxindole for Examples 36 and 37 is prepared in PREPARATION B, *infra*. The starting material oxindole for Examples 38 and 39 is prepared in PREPARATION C, *infra*. The starting material oxindole for Examples 40 and 41 is prepared in PREPARATION D, *infra*.

EXAMPLES 42-45

Following the method of Example 1, the following products were prepared by reacting an appropriate substituted benzaldehyde, in place of 3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxy benzaldehyde of Example 1, with oxindole. Unless otherwise indicated, the starting material benzaldehyde is either known in the literature or is commercially available. The wavy lines indicate that these compounds can exist as either the E or Z stereoisomers as indicated below.

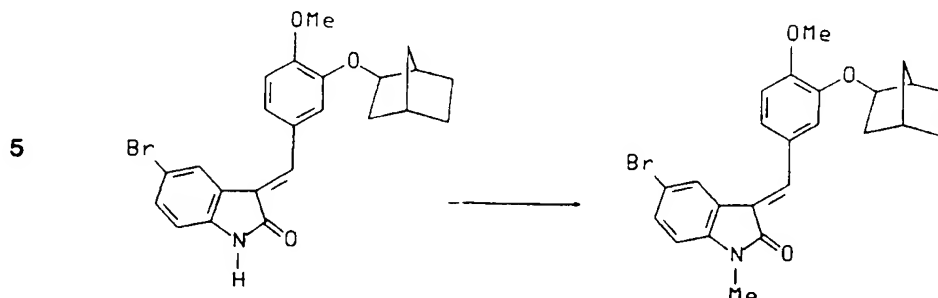


Ex.	R ¹	R ²	R ⁶	Stichm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
42	see R ²	CH ₂ CH ₂ (R ¹ and R ² connected)	H	E	203-205						C ₁₇ H ₁₃ NO ₃	Calc: 279.0895 Found: 279.0885
43	see R ²	CH ₂ CH ₂ (R ¹ and R ² connected)	H	Z	210-211		Calc: Found:	73.11 72.86	4.69 4.53	5.02 4.95		

Ex.	R ¹	R ²	R ⁰	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
44	Me	(CH ₂) ₄ C ₆ H ₅	H	E	185-186	C ₂₄ H ₂₈ NO ₃	Calc: Found:	78.17 78.05	6.31 6.22	3.51 3.48		
45	Me		Me	Z	219-221	C ₂₄ H ₂₈ NO ₃ • H ₂ O	Calc: Found:	73.26 73.34	8.92 6.49	3.55 3.51	C ₂₄ H ₂₈ NO ₃	Calc: 375.1834 Found: 375.18346

5 The starting material benzaldehyde for Example 44 is prepared in PREPARATION E, *infra*. The starting material benzaldehyde for Example 45 is prepared in PREPARATIONS F & G, *infra*.

EXAMPLES 46 & 47



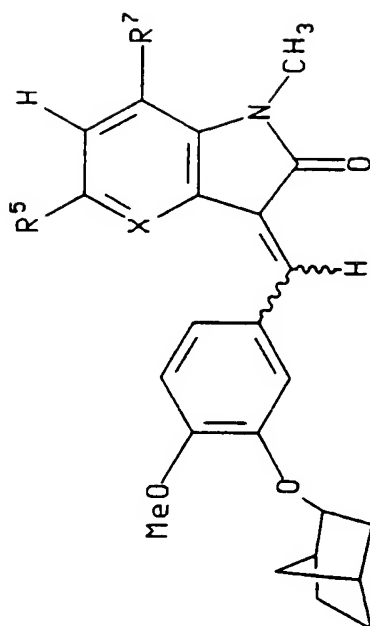
- 10 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one (Example 46) and 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one (Example 47)

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one (Ex. 16) (374 mg, 0.85 mmol) and potassium carbonate (177 mg, 1.28 mmol) were combined in 10 ml of acetone under an inert atmosphere. To this orange, heterogeneous mixture, was added 0.08 ml of methyl iodide (1.28 mmol) via syringe. The reaction was heated to 65° for 16 hours. The potassium carbonate was filtered off and washed well with CH₂Cl₂. The solvent was removed by rotary evaporation to yield a yellow oil which was purified via flash chromatography (1:1 Et₂O/hexane) to provide the desired methylated E isomer (89 mg, 23% yield) as a yellow, fluffy solid: mp 133-135° (Example 46). Analysis calculated for C₂₄H₂₄BrNO₃: C, 63.44; H, 5.32; N, 3.08. Found: C, 63.45; H, 5.22; N, 3.02. The corresponding Z adduct 3-[[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one was also obtained in 32% yield (124 mg) as a yellow solid (Example 47): mp 157-158°. Analysis calculated for C₂₄H₂₄BrNO₃: C, 63.44; H, 5.32; N, 3.08. Found: C, 63.22; H, 5.23; N, 3.08.

- 36 -

EXAMPLES 48-55

Following the method of Example 46 the following products were prepared by reacting the appropriate oxindole indicated below in place of the title compound of Example 16 with methyl iodide. The wavy lines indicate that these compounds can exist as either the E or Z stereoisomer as indicated below.



Ex	R ⁶	R ⁷	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
48	NO ₂	H	C-H	E	124-145	C ₂₂ H ₂₄ N ₂ O ₆ • 1/2H ₂ O	Calc: Found:	67.12 67.09	5.87 5.57	6.52 6.43	C ₂₂ H ₂₄ N ₂ O ₆	Calc: 420.1685 Found: 420.1699
49	NO ₂	H	C-H	Z	215-216	C ₂₂ H ₂₄ N ₂ O ₆ • 1/2H ₂ O	Calc: Found:	67.12 67.26	5.87 5.55	6.52 6.51	C ₂₂ H ₂₄ N ₂ O ₆	Calc: 420.1685 Found: 420.16823

-37-

Ex.	R ⁶	R ⁷	X	Stchm	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
50	NO ₂	NO ₂	C-H	E	212-216						C ₂₄ H ₂₃ N ₃ O ₇	Calc: 465.1536 Found: 465.1472
51	Cl	H	N	E	178-180	C ₂₃ H ₂₃ ClN ₂ O ₃	Calc: Found:	67.23 67.30	5.64 5.49	6.82 6.51		
52	Cl	H	N	Z	136-138	C ₂₃ H ₂₃ ClN ₂ O ₃	Calc: Found:	67.23 67.03	5.64 5.28	6.82 6.68		
53	H	H	N	E	153.8- 155.3	C ₂₃ H ₂₄ N ₂ O ₃	Calc: Found:	73.38 72.98	6.43 6.35	7.44 7.40		
54	Me	H	C-H	E	154-156	C ₂₈ H ₂₇ NO ₃	Calc: Found:	77.10 76.74	6.99 7.24	3.60 3.42		
55	OC ₆ H ₅	H	C-H	Z	semi- solid						C ₂₉ H ₂₃ NO ₄	Calc: 459.2410 Found: 459.2443

The starting material oxindole for Examples 48 and 49 is Example 26. The starting material oxindole for example 50 is Example 27. The starting material oxindole for Examples 51 and 52 is Example 28. The starting material oxindole for Example 53 is Example 29. The starting material oxindole for Example 54 is Example 30. The starting material oxindole for Example 55 is Example 63.

-38-

EXAMPLE 56

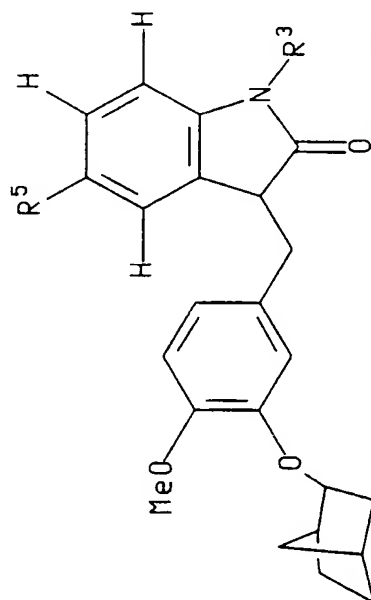
3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methyl]-1,3-dihydro-2H-indol-2-one. 3-[[3-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one (Example 3, 500 mg, 1.38 mmol) was dissolved 5 in 50 ml of ethyl acetate and 25 ml of tetrahydrofuran, placed in a Parr shaker with 180 mg of 10% palladium on carbon and shaken for 2 hours at 50 psi H₂. After filtering the reaction mixture through Celite, the solvent was stripped off and the resulting clear oil was recrystallized with 1:2 Et₂O/hexane to provide the title compound (447 mg, 89% yield) as a fine white powder: mp 157-158°. Analysis 10 calculated for C₂₃H₂₅NO₃•1/4H₂O: C 75.08; H 6.99; N 3.81. Found: C 75.25; H 6.85; N 3.85. M/z calculated for C₂₃H₂₅NO₃: 363.1834. Found 363.18699.

- 39 -

EXAMPLES 57-58

Following the method of Example 58, the following products were prepared by hydrogenating the appropriate oxindole indicated below in place of the title compound of Example 3.

5



10

15

Ex.	R ²	R ⁵	Catalyst	Solvent	mp (°C)	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
57	H	OH	10% Pd/C	EtOAc/T HF	188-188	C ₂₃ H ₂₈ NO ₄ • 1/4H ₂ O	Calc: Found:	71.95 71.94	6.69 6.59	3.65 3.62	C ₂₃ H ₂₈ NO ₄	Calc: 379.1784 Found: 380.18429
58	NO ₂	H	PtO ₂	EtOAc	foam						C ₂₄ H ₂₈ N ₂ O ₃	Calc: 392.2100 Found: 392.21327

20

The starting material oxindole for Example 57 is Example 10. The starting material oxindole for Example 58 is Example 49.

Example 59 & 60

3-[[3-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]2,3-dihydro-2-oxo-
[1 α ,2 α (E),4 α]-1H-indol-1-carboxylic acid, ethyl ester (Example 59) and 3-[[3-
Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]2,3-dihydro-2-oxo-
5 [1 α ,2 α (Z),4 α]-1H-indol-1-carboxylic acid, ethyl ester (Example 60)

The title compound of Example 3 (1.0 g, 2.77 mmol), ethyl chloroformate (10.0 ml), and potassium carbonate (770 mg, 5.6 mmol) were combined under an inert atmosphere. The reaction mixture was stirred at room temperature overnight and then at 100°C for 6 hours. The solvent was then stripped off and the resulting yellow oil
10 was purified via flash chromatography (1:1 ethyl ether/hexane) to provide the E isomer (82.6 mg, 7% yield) as bright yellow crystals (Example 59): m.p. 123-124°C. Analysis calculated for C₂₆H₂₇NO₅: C, 72.04; H, 6.28; N, 3.23. Found: C, 71.99; H, 6.20; N, 3.22. The corresponding Z isomer (Example 60) was also obtained in 16% yield: m.p. 60-70°C. Analysis calculated for C₂₆H₂₇NO₅: C, 72.04; H, 6.28; N, 3.23. Found:
15 C, 72.14; H, 6.09; N, 3.18.

Example 61

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-acetoxy-1,3-
dihydro-[1 α ,2 α (Z),4 α]-2H-indol-2-one

The title compound of Example 10 (1.0 g, 2.65 mmol) was combined with 10
20 ml of 2N NaOH solution and heated to 55°C. To this dark red, heterogeneous mixture was added 0.25 ml of acetic anhydride (2.65 mmol) via syringe. The reaction mixture was stirred at 55°C for 1 hour. The reaction mixture was then taken up in 200 ml H₂O, adjusted to pH 7.5 with 1N HCl, extracted with 3 x 150 ml ethyl ether, dried over MgSO₄, filtered, and the solvent stripped off. The resulting yellow-orange oil was
25 purified via flash chromatography (1:1 ethyl ether/hexane) to provide the title compound (57.8 mg, 5% yield) as a yellow-orange powder: m.p. 192-194°C. M/z calculated for C₂₅H₂₆NO₅: 419.1733. Found: 419.1731.

Example 62 & 63

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyl-1,3-dihydro-[1 α ,2 α ,(E),4 α]-2H-indol-2-one(Example 62) and 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyl-1,3-dihydro-[1 α ,2 α ,(Z),4 α]-2H-indol-2-one (Example 63)

The title compound of Example 10 (1.0 g, 2.65 mmol) was dissolved in 25 ml of DMF (dimethylformamide) under an inert atmosphere and cooled to 0°C. To this bright orange, homogeneous solution was added NaH (60% dispersion in oil, 225 mg, 5.63 mmol) in one portion. The reaction mixture was stirred for 1 hour at 0°C and cyclopentyl chloride (0.3 ml, 2.88 mmol) was then added via syringe. The reaction mixture was then stirred at room temperature for 10 hours. The solvent was removed by Kugelrohr distillation and the black residue was taken up in 500 ml of ethyl ether. The resulting solution was washed twice with 300 ml H₂O and once with 300 ml saturated brine solution, and then dried over MgSO₄. The solution was then filtered and the solvent was stripped off. The resulting purple oil was purified via flash chromatography (1:1 ethyl ether/hexane) to provide the E isomer (53 mg, 5% yield) as a bright red powder (Example 62): m.p. 186-187°C. Analysis calculated for C₂₈H₃₁NO₄•½H₂O: 73.98; H, 7.10; N, 3.08. Found: C, 74.26; H, 6.90; N, 3.06. M/z calculated for C₂₈H₃₁NO₄: 445.2253. Found: 445.2258. The corresponding Z isomer (Example 63) was also obtained in 11% yield: m.p. 190-191°C. Analysis calculated for C₂₈H₃₁NO₄: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.39; H, 7.16; N, 2.97. M/z calculated for C₂₈H₃₁NO₄: 445.2253. Found: 445.2229.

Examples 64 & 65

3-[[3-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyl-1,3-dihydro-1-ethyl-[1 α ,2 α ,(E),4 α]-2H-indol-2-one (Example 64) and 3-[[3-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyl-1,3-dihydro-1-ethyl-[1 α ,2 α ,(Z),4 α]-2H-indol-2-one (Example 65)

The title compound of Example 11 (1.06 g, 2.61 mmol), cyclopentanol (0.31 ml, 3.42 mmol) and triphenylphosphine (1.028 g, 3.92 mmol) were combined in 50 ml of tetrahydrofuran under an inert atmosphere. To this dark red homogeneous solution was added 0.62 ml of diethylazodicarboxylate (3.94 mmol) via syringe. The reaction mixture was stirred at room temperature for 72 hours. The solvent was then stripped off and the resulting orange oil was purified via flash chromatography (1:1 ethyl

-42-

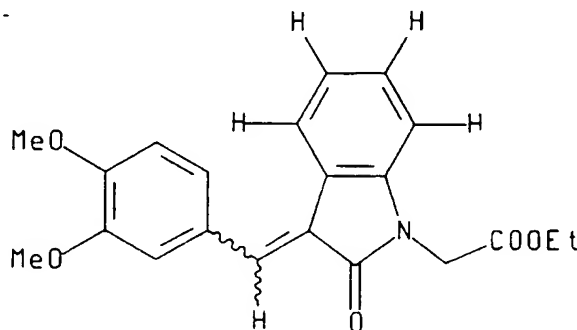
ether/hexane) to provide the E isomer (200 mg, 16% yield) as an orange foam (Example 64). Analysis calculated for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 76.32; H, 7.39; N, 2.90. The corresponding Z isomer (Example 65) was also obtained in 66% yield (821 mg) as an orange foam. Analysis calculated for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 76.07; H, 7.50; N, 3.00.

Example 663-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-2,3-dihydro-2-oxo-[1 α ,2 α (E),4 α]-1H-indole-1-acetic acid, ethyl ester

The title compound of Example 16 (287 mg, 0.65 mmol) and ethyl chloroacetate (0.07 ml, 0.77 mmol) were dissolved in 30 ml of DMF (dimethylformamide) under an inert atmosphere. The reaction mixture was cooled to 0°C whereupon 31.1 mg of NaH (60% dispersion in oil, 0.78 mmol) was added. The reaction mixture was stirred at 0°C for 20 minutes and then allowed to warm to room temperature. The reaction mixture was poured in 100 ml of H_2O , extracted with three 100 ml portions of ethyl ether, dried over $MgSO_4$, filtered, and the solvent stripped off. The remaining DMF was removed via Kugelrohr distillation and the resulting oil was purified via flash chromatography (1:1 ethyl ether/hexane) to provide the title compound (40 mg, 12% yield) as a yellow solid: m.p. 141-143°C.

EXAMPLES 67-68

Following the method of Example 66, the following products were prepared by reacting ethyl chloroacetate with the appropriate oxindole in place of the title compound of Example 16. The starting material oxindole is known in the literature. The wavy lines indicate that these compounds can exist as either the E or Z stereoisomers, as indicated below.



Ex.	Stchm.	mp (C°)	MF for Analysis	Anal.	C	H	N
67	E	143-144	C ₂₁ H ₂₁ NO ₅	Calc: Found:	68.65 68.21	5.76 5.59	3.81 3.98
68	Z	148-149	C ₂₁ H ₂₁ NO ₅	Calc: Found:	68.65 68.57	5.76 5.64	3.81 3.83

5

Example 693-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-amino-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one

The title compound of Example 49 (448 mg, 1.06 mmol) and iron powder (355 mg, 6.36 mmol) were combined in 9 ml of 1:1 ethanol/water and heated to 96°C under an inert atmosphere. To this yellow, heterogeneous mixture was added 0.03 ml of 12N HCl in 0.29 ml ethanol via syringe. The reaction mixture was stirred at 100°C for 1 hour, whereupon 1N NaOH solution was added until the pH was equal to 8. The iron was filtered off through a pad of diatomaceous earth (CELITE®). The pad was washed with water and then with ethyl acetate. The two layers were then separated, the organic layer was washed with 100 ml of saturated brine solution, dried over MgSO₄, filtered, and stripped to a red oil. This crude oil was purified via flash chromatography (ethyl ether) to provide the title compound (151 mg, 36% yield) as a red powder: m.p. 170-172°C. M/z calculated for C₂₄H₂₆N₂O₃: 390.1943. Found: 390.18906.

20

PREPARATIONSPREPARATION AN-methyl-5-methoxyoxindole

5-methoxy oxindole (450 mg, 2.76 mmol) and potassium carbonate (585 mg, 4.23 mmol) were combined in 45 ml of acetone under an inert atmosphere. To this white, heterogenous mixture was added 0.33 ml of methyl iodide (5.30 mmol) via syringe. The reaction mixture was stirred at room temperature for 10 hours and then at 75°C for 3 hours. Additional potassium carbonate and methyl iodide were added (290 mg and 0.11 ml, respectively), and the reaction mixture was stirred at 75°C for 6 more hours. The reaction mixture was then poured into 300 ml of saturated brine solution and extracted with 3 x 200 ml ether. The combined organic layers were dried over MgSO₄, filtered, and stripped to a yellow oil. This was purified via flash

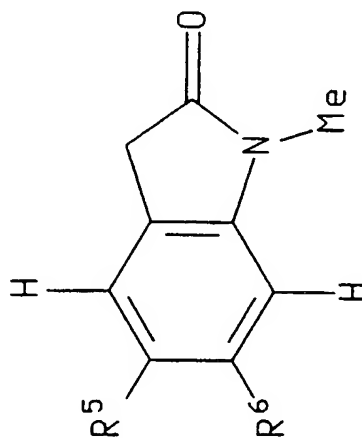
-44-

chromatography (3:1 ethyl ether/hexane) to provide the title compound (307 mg, 63% yield) as white crystals; m.p. 93-94°C. M/z calculated for $C_{10}H_{11}NO_2$: 177.0790, Found: 177.08066.

-45-

PREPARATIONS B & C

Following the method of Preparation A, the following products were prepared by reacting the appropriate oxindole with methyl iodide. The appropriate oxindoles are known in the literature.



Prep.	R ⁵	R ⁶	mp (°C)	To Form Ex. No.	MF for Analysis	Anal.	C	H	N	MF for m/z	m/z
B	H	OMe	96-98	36.37						C ₁₀ H ₁₁ NO ₂	Calc: 177.0790 Found: 177.0781
C	OMe	OMe	117-118	38.39	C ₁₁ H ₁₃ NO ₃	Calc: Found:	63.76 63.36	6.32 6.36	6.76 6.52	C ₁₁ H ₁₃ NO ₃	Calc: 207.0895 Found: 207.08961

PREPARATION D5-(N,N-dimethylsulfonamidyl)oxindole

To a suspension of AlCl_3 (108 g, 0.81 mol) in CS_2 (370 ml) was added dimethylsulfamoyl chloride (17.2 ml, 0.16 mol), followed by oxindole (17.6 g, 0.132 mol, ALDRICH). The reaction mixture was heated to reflux for 4.5 hours. The CS_2 solution was decanted off, leaving a gummy solid. The solid was scraped into crushed ice and stirred for 30 minutes. The solid was filtered to yield the title compound (9.3 g, 39% yield) as a tan solid: m.p. 208-215°C.

PREPARATION E10 4-Methoxy-3-(4-phenylbutyloxy)benzaldehyde

Following the method of Example 64, the title compound was prepared from 3-hydroxy-4-methoxybenzaldehyde (ALDRICH) and 4-phenyl-1-butanol (Aldrich). M/z calculated for $\text{C}_{18}\text{H}_{20}\text{O}_3$: 284.1412. Found: 284.1435.

PREPARATION F15 2-(3-[3-(Bicyclo[2.2.1]hept-2-yloxy)]-4-methoxyphenyl)-2-hydroxyethane

3-(*exo*-Bicyclo [2.2.1] hept-2-yloxy)-4-methoxybenzaldehyde (as disclosed in WO 87/06576 published November 5, 1987) (7.0 g, 28.4 mmol) was dissolved in 100 ml of tetrahydrofuran under an inert atmosphere and cooled to 0°C, whereupon 10.42 ml of 3.0M methyl magnesium bromide in ethyl ether was added via syringe. The reaction mixture was stirred at 0°C for 1 hour and then at room temperature for 1 hour. The reaction mixture was slowly poured into a mixture of 500 ml of saturated brine solution and 500 ml of ethyl ether. The layers were separated and the aqueous layer was extracted with two 300 ml portions of ethyl ether. The combined organic layers were dried over MgSO_4 , filtered and stripped to a yellow oil. This was purified by flash chromatography (2:1 hexane/ethyl ether) to provide the title compound (4.98 g, 67% yield) as a yellow solid: m.p. 60-61.5°C. Analysis calculated for $\text{C}_{18}\text{H}_{22}\text{O}_3$: C, 73.25; H, 8.45. Found: C, 73.54; H, 8.59. M/z calculated for $\text{C}_{18}\text{H}_{22}\text{O}_3$: 262.1569. Found: 262.1564.

PREPARATION G30 Aceto-(3-[3-bicyclo[2.2.1]hept-2-yloxy])-4-methoxy)phenone

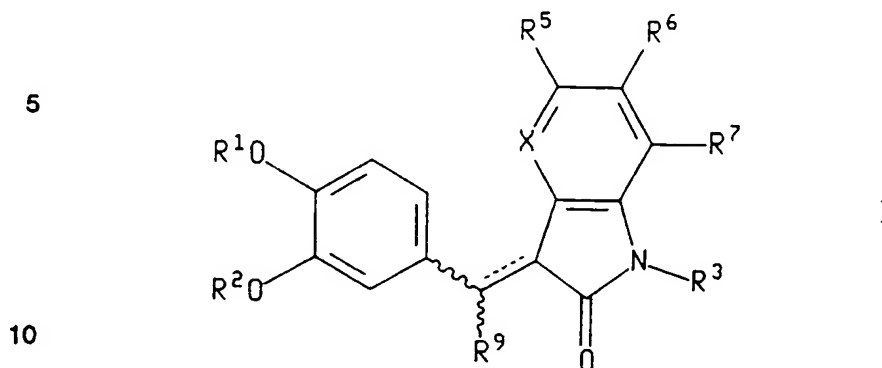
The title compound of Preparation F (4.98 g, 19 mmol) and 27 ml of H_2O were combined and cooled to 0°C. To this yellow suspension was added 2.17 ml of concentrated sulfuric acid. Acetone (103 ml) was then added and the reaction mixture

-47-

was stirred at 0°C until the mixture became homogeneous. Finally, 27.1 ml of Jones reagent was added rapidly by syringe, whereupon the reaction mixture was stirred at 0°C for 15 minutes and room temperature for 1 hour. The reaction mixture was then slowly poured into 500 ml saturated bicarbonate solution and stirred for 15 minutes
5 at room temperature. This mixture was extracted with three 300 ml portions of ethyl ether and once with 300 ml CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and stripped to a yellow oil. This crude material was recrystallized in 150 ml warm hexane to yield the title compound (4.19 g, 85% yield) as light brown crystals: m.p. 95-97°C. Analysis calculated for C₁₆H₂₀O₃: C, 73.82; H, 7.74. Found:
10 C, 73.73; H, 7.65. M/z calculated for C₁₆H₂₀O₃: 260.1412. Found: 260.1404.

CLAIMS

1. A compound of the formula:



wherein X is N or CR⁴:

R' is (C₁-C₄) alkyl or phenyl-(C₁-C₈) alkyl;

R² is (C₁-C₁₀) alkyl, phenyl-(C₁-C₈) alkyl, (C₃-C₇) cycloalkyl, or (C₆-C₁₂)

15 polycycloalkyl;

or R¹ and R², taken together with the oxygens to which they are attached, represent a methylene or ethylene bridge which forms a 5 or 6 membered ring;

R^3 is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkyloxycarbonyl, (C_1-C_6) alkyloxy, (C_1-C_6) alkoxy carbonyl- (C_1-C_6) alkyl, $-CONR^{10}R^{11}$; or $-(C_1-C_6)$ alkyl- $CONR^{10}R^{11}$;

20 R¹⁰ and R¹¹ are independently selected from hydrogen and (C₁-C₆) alkyl, or R¹⁰ and R¹¹, taken together with the nitrogen to which they are attached, form a pyrrolidine or piperidine ring;

R^4 , R^5 , R^6 and R^7 are independently selected from hydrogen, halogen, (C_1-C_6) alkoxy, (C_3-C_7) cycloalkyloxy, hydroxy, (C_2-C_6) acyloxy, nitro, NR^8R^{12} , $SO_2NR^8R^{12}$, (C_1-C_6) alkyl, (C_1-C_6) alkylcarbonyl, phenyl- (C_1-C_6) alkoxy, and (C_6-C_{12}) polycycloalkoxy or any combination of R^4 and R^5 , R^5 and R^6 , or R^6 and R^7 which together form $-OCH_2O-$ or $-OCH_2CH_2O-$, such that, when taken together with the carbons to which they are attached, they form, respectively, a 5- or 6-membered ring;

R^8 and R^{12} are independently selected from hydrogen and (C₁-C₆) alkyl, or R^8 and R^{12} , taken together with the nitrogen to which they are attached, form a pyrrolidine or piperidine ring;

R^9 is hydrogen or (C_1-C_6) alkyl;

the broken line represents an optional double bond; and

the wavy lines indicate that the compounds exist as (E) and/or (Z) stereoisomers when the broken line is a double bond;

with the proviso that (a) if R¹ and R² are both methyl, X is CH, R⁹ is hydrogen, and the broken line is a double bond, then (i) at least one of R³, R⁵, R⁶, and R⁷ is
 5 other than hydrogen; (ii) at least one of R⁵, R⁶ and R⁷ is other than hydrogen or R³ is other than methyl; and (iii) at least one of R³ and R⁷ is other than hydrogen or at least one of R⁵ and R⁶ is other than O-CH₃; (b) if R³ is hydrogen, R⁹ is hydrogen, X is CH, the broken line is a double bond, and R¹ and R² together represent a methylene
 10 are both methyl, X is CH, R⁹ is hydrogen, and the broken line is a single bond, then at least one of R⁵ and R⁶ is other than O-CH₃, or R⁷ is other than hydrogen, or R³ is other than COCH₃;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein:

15 R¹ is methyl or ethyl and R² is (C₁-C₆) alkyl, phenyl-(C₁-C₆) alkyl, (C₃-C₇) cycloalkyl, or (C₆-C₁₂) polycycloalkyl; or

R¹ and R², taken together with the oxygens to which they are attached, represent a methylene or ethylene bridge which forms a 5 or 6 membered ring.

3. A compound according to claim 1 wherein X is CH or N, R¹ is methyl,
 20 R² is norbornyl, R³ is hydrogen, methyl, ethyl, -COOC₂H₅, -CONH₂, methoxy or -CH₂COOC₂H₅, R⁶ is hydrogen, bromo, methoxy or chloro, and R⁵ is hydrogen, hydroxy, cyclopentyloxy, methoxy, bromo, chloro, amino, or -SO₂NH₂, or R⁵ and R⁶ together form -OCH₂O-, R⁷ is hydrogen, and R⁹ is hydrogen or methyl.

4. A compound according to claim 1 selected from the group consisting
 25 of:

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-ethyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

30 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-1,3-dihydro-1-ethyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-chloro-1,3-dihydro-1-methoxy-[1 α ,2 α (Z), 4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-chloro-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

5 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-bromo-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-chloro-1,3-
10 dihydro-1-methyl-[1 α ,2 α (Z),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-5-cyclopentyloxy-1,3-dihydro-1-ethyl-[1 α ,2 α (E),4 α]-2H-indol-2-one;

3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-6-methoxy-1,3-dihydro-1-methyl-[1 α ,2 α (E),4 α]-2H-indol-2-one; and

15 3-[[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]methylene]-2,3-dihydro-N,N-dimethyl-2-oxo-[1 α ,2 α (E),4 α]-1H-indole-5-sulfonamide.

5. A pharmaceutical composition for treating a condition selected from the group consisting of acquired immunodeficiency syndrome ("AIDS"), asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease,
20 psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising an amount of a compound of claim 1, effective in treating such a condition, and a pharmaceutically acceptable carrier.

6. A method of treating a condition selected from the group consisting of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive
25 airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

7. A pharmaceutical composition for inhibiting the effects of
30 phosphodiesterase type IV in a mammal, including a human, comprising a phosphodiesterase type IV inhibiting amount of a compound of claim 1, and a pharmaceutically acceptable carrier.

-51-

8. A method of inhibiting the effects of phosphodiesterase type IV in a mammal, including a human, comprising administering to said mammal a phosphodiesterase type IV inhibiting amount of a compound of claim 1.

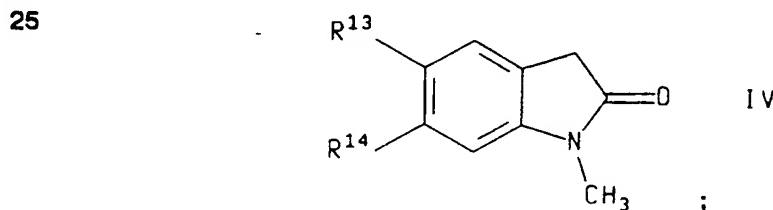
9. A pharmaceutical composition for treating a condition selected from the group consisting of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising an amount of a compound of claim 1, effective in inhibiting the action of phosphodiesterase type IV, and a pharmaceutically acceptable carrier.

10. A method of treating a condition selected from the group consisting of AIDS, asthma, rheumatoid arthritis, osteoarthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, atopic dermatitis, shock, and other inflammatory diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in inhibiting the action of phosphodiesterase type IV.

11. A pharmaceutical composition for treating a disorder in a mammal, including a human, the treatment of which is effected or facilitated by blocking the action of phosphodiesterase type IV, comprising an amount of a compound of claim 1, effective in treating such disorder, and a pharmaceutically acceptable carrier.

12. A method of treating a disorder in a mammal, including a human, the treatment of which is effected or facilitated by blocking the action of phosphodiesterase type IV, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a disorder.

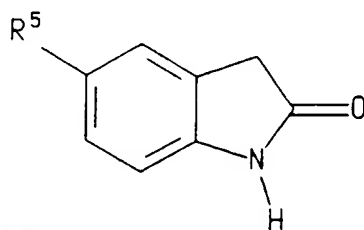
13. A compound of the formula:



30 wherein R¹³ and R¹⁴ are independently selected from hydrogen and methoxy.

14. A compound of the formula:

-52-

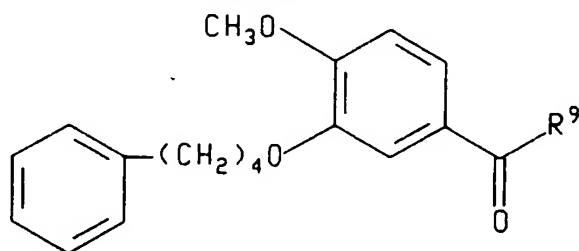


V

5

wherein R^5 is $SO_2NR^8R^{12}$.

15. A compound of the formula:



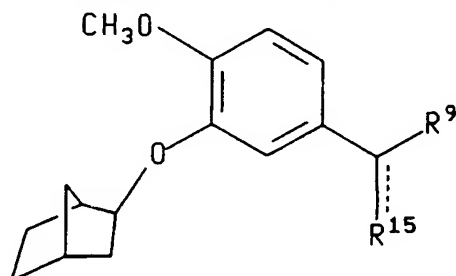
VI

10

wherein R^9 is hydrogen or (C_1-C_6) alkyl.

15

16. A compound of the formula:



VII

20

wherein R^9 is hydrogen or (C_1-C_6) alkyl, R^{15} is oxygen or hydroxy, and the broken line represents a double bond when R^{15} is oxygen.

INT. NATIONAL SEARCH REPORT

International Application No

PCT/IB 94/00312

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D209/34 A61K31/395 C07D491/04 C07D471/04 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol.36, no.22, 29 October 1993, WASHINGTON US pages 3274 - 3277 P.W. BAURES '... phosphodiesterase inhibitory activity of ...' * page 3274 *	1,7
A	US,A,5 124 347 (WARNER-LAMBERT COMPANY) 23 June 1992 * column 1-2 *	1,5
A	EP,A,0 164 860 (PFIZER INC.) 18 December 1985 * page 1-4 *	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

28 November 1994

Date of mailing of the international search report

30. 11. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

national application No.

PCT/IB 94/00312

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6,8,10 and 12 are directed to method of treatment of
(diagnostic method practised on) the human/animal body, the search has been
carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

IN NATIONAL SEARCH REPORT

Information on patent family members

Patent Application No

PCT/IB 94/00312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5124347	23-06-92	NONE	
EP-A-0164860	18-12-85	US-A- 4569942	11-02-86
		AU-B- 554290	14-08-86
		AU-A- 4193885	07-11-85
		BG-B- 60208	30-12-93
		BG-B- 60207	30-12-93
		CA-A- 1255658	13-06-89
		EP-A, B 0244918	11-11-87
		JP-C- 1672307	12-06-92
		JP-B- 3035315	27-05-91
		JP-A- 60243068	03-12-85
		QA-A- 8098	31-03-87
		SU-A- 1468413	23-03-89

